REMARKS

The Office Action sent April 1, 2009 has been received and reviewed. All claims currently under consideration stand objected to or rejected. All amendments are made without prejudice or disclaimer. Support for the amendments and new claim can be found throughout the published Specification, for example, in at least paragraphs **[0009]-[0010]**, **[0045]**, **[0056]**, **[0063]**, **[0064]**, **[0045]**, **[0081]** and the claims as previously presented. Accordingly, no new matter has been added. Reconsideration is respectfully requested.

Sequence Compliance

In response to the Office's comments with regard to Sequence Compliance, applicants respectfully reference the substitute Specification submitted February 17, 2005, wherein paragraph **[0021]** references the sequences depicted in Figure 1 as being SEQ ID NO:6. As the sequences were originally submitted in both electronic and paper format no substitute sequence listing should be needed.

Additionally, the Office commented on amino acid sequences disclosed in the Specification for example, at page 6, lines 6-7. Applicants believe that in light of the "Definitions of Nucleotide and/or Amino Acids for Purposes of Sequence Rules" found in MPEP §§ 2421.02 and 2422.01, the instant Specification's reference to sequences such as those at page 6, lines 6-7, do not necessitate a SEQ ID NO. For example, § 2421.02 states:

> "[t]he sequence rules embrace all unbranched nucleotide sequences with ten or more bases and all unbranched, non-D amino acid sequences with four or more amino acids, provided that there are at least 4 "specifically defined" nucleotides or amino acids." MPEP § 2421.02, emphasis added.

In light of the non-specific description of those sequences in the Specification, *e.g.*, at page 6, lines 6-7, applicants believe that identification of those sequences are not required as defined by MPEP §§ 2421.02 and 2422.01.

Claim Objections

Claim 47 stands objected to due to a typographical error. The claims have been appropriately amended.

35 U.S.C. § 112, 2nd Paragraph

Claims 1, 3, 27, and 46-48 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants have amended the claims to reference the appropriate SEQ ID NO.

Claims 1, 46, and 48 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly omitting essential steps. Applicants note with appreciation the suggestion by the Office and have amended the claims appropriately.

Claim 3, 27, and 47 stand rejected under 35 U.S.C § 112, second paragraph, as allegedly omitting essential steps. Applicants note with appreciation the suggestion by the Office and have amended the claims appropriately.

Claim 47 stands rejected under 35 U.S.C § 112, second paragraph, as lacking sufficient antecedent basis. Claim 47 has been appropriately amended.

35 U.S.C. § 112, 1st Paragraph

Claims 1-4, 8-10, 27-30, and 46-48 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the Written Description requirement. Specifically, the Office alleges that the genus of nucleotide sequences that encode the indicated protein fragment of the protein of Fig.1 has a substantial variance, which variance is allegedly insufficiently described by the Specification. *See,* Office Action, page 8, The Office further alleges that experimentation would be required to determine which sequences could be used, since no precise sequence are disclosed and the nature of applicants' claimed methods are unpredictable. *Id.* Applicants respectfully traverse the rejection.

Claims 1-3, 27-28, and 46-48 have been amended to recite, in part, "wherein said ectodomain comprises amino acid sequence 25-545 of SEQ ID NO:7, and wherein the fragment thereof comprises an amino acid sequence selected from the group consisting of 25-442, 97-442, and 97-545 of SEQ ID NO: 7." Applicants submit that in view of these amendments, the claimed methods are in compliance with the Written Description requirement. For example, the *Plasmodium falciparum* AMA-1 ectodomain is expressly claimed as comprising amino acid sequence 25-545 of SEQ ID NO:7. Applicants note that SEQ ID NO: 7 is not only illustrated in the sequence listing but also in FIG. 1. The ectodomain is further described in paragraphs

[0009]-[0010] of the published application. *See* Published Specification, paragraphs **[0009]-[0010]**.

Applicants additionally submit that the *Plasmodium falciparum* AMA-1 ectodomain fragments, as presently included in the claimed methods, are in compliance with the Written Description requirement, as the fragments are expressly claimed as comprising amino acid sequences 25-442, 97-442, or 97-545 of SEQ ID NO: 7.

Applicants further submit that, contrary to the Office assertions and in view of applicants' remarks presented in the response of July 3, 2008, which are incorporated by reference herein, the claimed fragments are sufficiently described by both structure and a correlation with the described structure and function. As previously noted, fragment structures are expressly claimed, to wit, "wherein the fragment thereof comprises an amino acid sequence selected from the group consisting of 25-442, 97-442, and 97-545 of SEQ ID NO: 7." Additionally, at least one exemplary nucleotide sequence for each of the three fragments are structurally disclosed in SEQ ID NO:6 and FIG. 1. The disclosed structures and sequences are further described in terms of function, to wit, "wherein said *Plasmodium falciparum* AMA-1 ectodomain fragment exhibits specificity for mAb 4G2."

The Office alleges that "the claims lack written description for that which encompasses critical sequences that are not known but which require experimentation to obtain due to the unpredictable nature of applicants' invention." Office Action, page 8. Applicants respectfully disagree.

The Specification describes amino acid residues that are important for such specificity for mAb 4G2. Paragraphs **[0056]-[0062]** of the published Specification describe experimental data that indicate that Pf3mH (presently claimed residues 25-442), Pf4mH, and Pf14-0 (presently claimed residues 97-545) showed specificity with mAb 4G2, while others, such as Pf10mH, Pf9mH, etc. did not." *See* Specification at paragraphs **[0056]-[0062]**. The experimental data in the Specification shows that the epitope for mAb 4G2 was mapped to domain I or domain I+II. *Id.* The Specification additionally describes residues 97-442 as including domains I and II. *Id.* Thus, the Specification demonstrates that the fragments, 25-442, 97-442, and 97-545, as presently recited in the claims, are important necessary for specificity with mAb 4G2, as presently claimed.

The Office alleges that "the claims lack written description due to the unpredictable nature of applicants' invention." Office Action, page 8. Again applicants respectfully disagree. Specifically, the Office has cited Fandeur et al. (of record, hereinafter Fandeur). Fandeur teaches that two different variants of the Palo Alto strain of *Plasmodium falciparum* resulted in a different immune response. Fandeur, abstract. The Office alleges that there can be strain specific or host specific immunity in a simian species infected with *Plasmodium falciparum. Id.* Applicants submit that this suggests, at the very most, the existence of some unpredictability between strains of Palo Alto strains of *Plasmodium falciparum* with regard to immunity for among different host or strains. Furthermore, Fandeur provides no apparent suggestions of unpredictability in AMA1 variants or in producing a properly folding protein. Applicants' claims are related to methods for producing AMA-1 proteins and mRNA. As such, the teachings of Fandeur are not relevant.

Furthermore, even if Fandeur was relevant, which applicants dispute herein, any unpredictability between Palo Alto strains of *Plasmodium falciparum* is lessened in view of the Fandeur's disclosure that in several cases, pervious or concomitant heterologous infections indicated a degree of cross protection between the strains. *Id.* Moreover, Fandeur states that the monkey immune response to infection transcends phenotype antigenic variation and strain diversity. *Id.* Thus, even if Fandeur were relevant to the instant case, Fandeur at most suggests that while there may be some different effects by variants of different strains, there is predictability that transcends strain diversity.

Applicants submit that in view of the preceding paragraph, at most Fandeur suggests minimal unpredictability between two strains of one type of *Plasmodium falciparum.* As previously stated, such a reference is, at most, distantly relevant if at all relevant to the currently claimed methods, as the claimed methods are directed to fragments of the AMA1 ectodomain. Furthermore, applicants have submitted herewith the following references (submitted in the enclosed IDS) which demonstrate and/or suggest the ability of recombinant expression of polymorphic and/or claimed fragments of *ama*1 to yield properly folded proteins.

- Remarque, E. J. et al. (2008), Infect. Immun. 76:2660-2670;
- Malkin, E. M. et al. (2005), Infect. Immun. 73:3677-3685; and

- Kennedy, M.C. et al. (2002), Infect. Immun. 70:6948-6960.

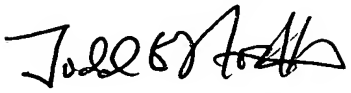
As can be understood from the above references and the as-filed Specification, exploiting PCR primer sets presented in the as-filed Application, *ama1* nucletoide sequences can be amplified from any *P. falciparum* strain or field isolate containing uncharacterized nucleotide polymorphisms. These nucleotide sequences can be optimized for *Pichica pastoris* codon usage (with deletion of potential glycosylation sites) according to the methods provided in the Specification, cloned into *P. pastoris* expression vectors and properly folded recombinant protein can be produced and purified following method described in the Application, without the need to have prior knowledge on the exact nature of the nucleotide polymorphisms and/or fragments. It is thus submitted that the presented claimed methods would more easily yield properly folded AMA1 proteins by following the methodology as presently claimed and described by the application. It is acknowledged that slight differences in antigeneity between the thus obtained proteins and the protein obtained by using the nucleotide sequences of Fig. 1 would be present, but these do not hamper the usability of the produced protein for an exemplary purpose in, *e.g.*, a vaccine.

In view of the foregoing, applicants submit that the claimed methods are sufficiently described by the Specification, as the claimed methods include multiple and express recitations of structure, such structure is demonstrated by the Specification as being important for functionality (*e.g.,* specificity for mAb4G2), and as the evidence of record suggests there exists a degree of predictability such that a person of ordinary skill in the art could recognize applicants were in possession of the claimed fragments. Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In light of the above amendments and remarks, the application should be in condition for allowance. If questions remain after consideration of the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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Enclosures: Supplemental Information Disclosure Statement
Petition for 1-month Extension of Time
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